Remarks

Submission of Sequence Listing and Amendment to Claims

The specification has been amended to insert the appropriate sequence identifiers.

Declaration under 37 C.F.R. § 1.821(f)

I declare that the material on the compact disc is identical to the paper copy of the Sequence Listing, that the Sequence Listing does not add new matter to the application, and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Objection to the Title and Restriction Requirement

It is believed that the title is highly descriptive of the claimed invention, and has therefore not been amended at this time. The appropriateness of the title will be reconsidered once the claims have been determined to be allowable. The examiner's attention is drawn to the previous restriction requirement and applicants' response, noting that if the composition claims are found allowable, the method claims may be rejoined and examined.

Objection to Claim 18

Claim 18 has been amended as suggested by the examiner, whose helpful suggestion is appreciated.

Rejection Under 35 U.S.C. §112, first paragraph-written description

Claims 16-23 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed

invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The examiner is confusing the claimed invention, which is, an organism and method of use, incorporating known genes in a new combination and new method. The claims are not drawn to new genes or a new genus of enzymes. The individual components of the claimed combinations and methods of use are all known. All that is required is to be told to make the claimed combinations; the components are readily available. It is well-established that in such cases it is more than adequate to provide representative sources for materials, so long as the selection criteria and instructions on how the materials are to be used are clearly taught by applicants.

The Legal Standard

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." *See* M.P.E.P. § 2163(I). All that is required is that the specification provides sufficient description to **reasonably** convey to those skilled in the art that, as of the filing date sought, that the inventor was in possession of the claimed invention. *Union Oil of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000); *Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant may show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. M.P.E.P. § 2163(I), citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 66, 48 USPQ2d 1641, 1646 (1998).

In a recent decision by the Board of Patent Appeals and Interferences, the Board warned that it is an improper analysis to determine that the claims are directed to an invention which is broader than that which is described in the specification since the written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-64. Thus the Board re-emphasized that the specification need not always spell out every detail; only enough "to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation." *LizardTech Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1344-34, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

Analysis

From the thorough description in the specification, it is clear that the Applicants were in possession of the claimed subject matter.

CoA-dependent dehydrogenase

CoA-dependent dehydrogenase is well known in the art, and the specification from page 9, line 13, to page 10, line 8, extensively describes different organisms that can serve as sources for CoA-dehydrogenase, along with gene bank accession numbers and a source for the sequences

of known CoA-dependent aldehyde dehydrogenases in various species (please see page 10, lines 27-30).

PHA Synthases

Genes involved in PHA synthesis as well as their sources are known in the art (*see* page 3, lines 9-12 of the specification; *see also* Madison and Huisman, *Microbiol. Mol. Bio. Rev.* 63(1):21-53 (1999) ("Madison"), and U.S. Patent 5,250,430 to Peoples, et al., ("Peoples"), submitted in the IDS filed December 23, 2003). Madison discloses genes encoding PHA synthases from *R. eutropha, P. oleovorans, and Synechocystis sp.* (*see* Madison, Figure 2). Peoples disclose PHA synthases from *Zoogloea ramigera, Alcaligenes eutrophus, Nocardia salmonicolur,* and *Pseudomonas oleovorans* (Peoples, abstract). Methods for identifying genes via complementation, including genes encoding PHA synthases are well-known to those skilled in the art (*see e.g.,* Nishikawa, et al., *Curr. Microbiol.* 44(2):132-135 (2002) (a copy of which is attached)).

Acyl CoA synthetase

Acyl CoA synthetase activity is referenced in Figure 1 of the specification. Genes encoding acyl CoA synthetase activity are were well-known to those skilled in the art. *See e.g.,* Black, et al., *J. Biol. Chem.* 267:25513-25520 (1992) ("Black"); van Beilen, et al., *Molecular Microbiology* 6:3121-3136 (1992) ("van Beilen"); and Matesanz, et al., *J. Mol. Biol.* 291:59-70 (1999) ("Matesanz"), copies of which are attached. Black discloses the *fadD* gene of *Escherichia coli* encoding acyl coenzyme A synthetase activity (Black, page 25513, abstract). van Beilen discloses *alkK* gene of *Pseudomonas olevorans* encoding acyl coenzyme A synthetase activity (van Beilen, page 3121, abstract). Matesanz discloses the *pfacs1* gene from *Plasmodium falciparum* encoding acyl coenzyme A synthetase activity (Matesanz page 59,

abstract). As described above, methods for identifying genes via complementation, including genes encoding acyl CoA synthetase activity, are well known to those skilled in the art.

Acyl CoA transferase

Acyl CoA transferase activity is depicted in Figure 1. Genes encoding acyl CoA transferase activity are well known to those skilled in the art. *See e.g.*, Madison, and Sohling, et al., *J. Bacteriol.* 178:871-880 (1996) ("Sohling") (a copy of which is attached). Sohling discloses the *cat1* gene encoding acyl CoA transferase activity from *Clostridium kluyveri* (Sohling, page 871, abstract). Sohling also states that CoA transferases from *Pseudomonas putida*, *Acinetobacter calcoaceticus, Clostridium acetobutylicum*, and from the pig heart have been identified (Sohling, page 878, col. 1). Madison reviews the pathways involved in engineering PHAs. Madison discloses genes encoding acyl CoA transferase activity including the *hbcT* gene from *Clostridium kluyveri* (*see* Madison, Figure 4). Methods to identify genes encoding acyl CoA via complementation, including genes encoding acyl CoA synthetase activity are well known to those skilled in the art.

As affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art. Therefore, claims 16-23 satisfy the written description requirement.

Rejection Under 35 U.S.C. §112, first paragraph-enablement

Claims 16-23 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Applicants respectfully traverse this rejection.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under §112, first paragraph, as whether one skilled in the art could make and use the

claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g., Amgen v. Hoechst Marion Roussell*, 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d 1361, 1365, 42 USPQ2d1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). *See also In re Fisher*, 427 F.2d, 833, 839, 166 USPQ 18, 24 (CCPA 1970); *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. *See Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F3d 956, 965-966, 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). In addition, a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *citing Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. *See In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art,

the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). **There is no requirement for examples**. The Supreme Court also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling *In re Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts."). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. MPEP § 2164.01(b).

In *In re Douglas v. United States* 510 F.2d 364, 184 U.S.P.Q. 613 (Ct. Cl.1975) the Court of Claims noted that a patentee cannot "be expected to foresee every technological problem that may be encountered in adapting his idea to a particular use. Some experimentation and exercise of judgment is to be expected." Further, the Federal Circuit noted in *In re Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening." *In re Wands*, citing *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916), wherein the court emphasized that some inventions cannot be practiced without adjustments being made to adapt them to the particular context. In such a situation, a specification is sufficient if it gives adequate guidance to one skilled in the art on how such adjustments are to be made.

Analysis

Genetically engineered plants and bacteria that make polyhydroxyalkanoates are known, having been described in the patent literature since **1989, i.e., for almost twenty years**. The problem applicants were addressing is how to produce recombinant organisms that can produce *high levels of medium chain length polyhydroxyalkanoates* (*see* page 3, line 27 to page 4, line 3 and page 8, lines 27-30) while avoiding increasing the level of 3-hydroxyacid in the feed, avoiding the use of 3-propionic acid in the feed, and avoiding the generation of free propionic acid in the cytosol. The solution, as described on page 4, lines 5-15, page 8, line 27 to page 9, line 12, and defined by the claims, is to provide, in addition to the other enzymes for polyhydroxyalkanoate production (beta-ketothiolase, acetyl CoA reductase and PHA synthase, all of which are known), a CoA aldehyde dehydrogenase which directly converts any aldehydes generated from the alcohols used as co-feed, into the corresponding acyl-CoA.

The claims define a recombinant organism for producing polyhydroxyalkanoate, selected from the group consisting of bacteria, yeast, fungi and plants, comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and a PHA synthase. The organism further comprises a gene encoding acyl-CoA tranferase, acyl-CoA synthetase, β-ketothiolase, and acetacetyl Co-A reductase. As stated previously, Co-A-dependent aldehyde dehydrogenase and PHA synthase are well known in the art, although not in the claimed combination for the purpose of making medium chain length polyhydroxyalkanoates. As discussed above, the specification from page 9, line 13, until page 10, line 8 extensively describes different organism that can serve as sources for CoA-dehydrogenase, providing gene bank accession numbers and a source for the sequences of known CoA-dependent aldehyde dehydrogenases in various species (*see* page 10, lines 27-30). Genes and techniques for developing recombinant PHA producers are known in

the art (*see* Madison). Once a gene is identified, it is routine in the art to incorporate the gene into a plasmid, or the chromosome, for expression in the cells.

There is sufficient guidance in the specification to construct plasmids and express the claimed genes (*see* Examples in the pending application). In addition, the experimental protocols are routine and expression vectors, restriction enzymes and ligation enzymes are commercially available. Although there is no need for examples, Applicants **have provided examples** to show that one can isolate, identify and express the enzymes in organisms as recited in the claims. Example 1 shows the amplification and expression of the eutE gene in *E. coli*. It is important to understand that *E. coli* do not normally make PHAs. Example 3 shows successful production of PBHV by *E.coli* expressing eutE and PHB synthesis genes. Based on the teachings in the specification, and the state of the art, one of ordinary skill in the art would be able to make a recombinant organism as claimed by Applicants that is capable of producing PHAs.

Patents are not required to disclose every species encompassed by the claims, even in an unpredictable art. *In re Vaeck,* 947 F.2d 488, (Fed. Cir. 1991). As set forth in *Johns Hopkins Univ. v. CellPro Inc.,* 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998), "the enablement requirement is met if the description enables **any** mode of making and using the invention." All of the genes to be incorporated into the recombinant organism claimed by the Applicants are well known in the art and Applicants have provided numerous working examples of recombinant *E. coli* producing a medium chain PHA as claimed. The art discussed above and in the specification demonstrates that the results in bacteria are predictive of the results in plants, and that the same genes can be integrated into the plants for production of PHA. It is very clear from the disclosure in the specification and the state the art, that a skilled artisan would be able

to make recombinant bacteria, yeast, fungi and plants that express all the genes that are recited in the claims. Therefore, claims 16-23 are enabled.

Rejection Under 35 U.S.C. § 102

Claims 16 and 22 were rejected under 35 U.S.C. § 102(b) as anticipated by Toth, et al., *Appl. Environ. Microbiol*, 65(11):4973-80 (1999) ("Toth"). Applicants respectfully traverse this rejection. Claim 16 has been amended to recite the limitation of claim 17.

The Legal Standard

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc. v Monoclonal Antibodies Inc.*, 231 USPQ 81 (Fed. Cir. 1986); *Scripps Clinic & Research Found. v Genentech Inc.*, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*:

Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. There must be *no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (18 USPQ2d at 1010, emphasis added).

Further, a reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation (*see Id.*).

Analysis

Toth discloses the purification of the CoA-acylating aldehyde dehydrogenase (ALDH) from the solvent-producing organism *Clostridium beijerinckii* NRRL B593. Alignment of the amino acid sequences of ALDH from *Clostridium beijerinckii* NRRL B593 revealed that the

amino acid sequence of ALDH of *Clostridium beijerinckii* NRRL B593 was most similar to those of eut E and *E. coli*. Applicant's amended claims define a recombinant organism selected from the group consisting of bacteria, yeast fungi and plants, comprising a heterologous gene encoding a CoA-dependent aldehyde dehyrogenase and PHA synthase. Toth does not disclose a recombinant organism comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and a PHA synthase. Therefore claims 16 and 22 are novel over Toth.

Rejection Under 35 U.S.C. § 103

Claims 16-20 and 22-23 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,329,183 to Skraly, et al. ("Skraly"), in view of Toth. Claims 16-20, 21 and 22-23 were rejected as obvious over Skraly, in view of Goodlove, et al., *Gene*, 85:209-214 (1989) ("Goodlove"). Applicants respectfully traverse these rejections.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967); *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992); *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

It is clear that to establish a rejection under 35 U.S.C. §103 the cited references must (1) recite each element of the claims, (2) provide one of skill in the art with the motivation to modify the cited reference and (3) provide one of ordinary skill in the art with a reasonable expectation of success. Neither Skraly nor Toth either alone or in combination meet all three criteria.

Skraly in view of Toth

Skraly discloses organisms which express enzymes such as glycerol dehydrogenase, diol dehydratase, acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, PHA synthase, glycerol-3-phosphate dehydrogenase, and glycerol-3-phosphatase, which are useful for the production of PHAs. Skraly also discloses that genes encoding a vicinal diol dehydratase, a PHA synthase, and optionally, an aldehyde dehydrogenase, 1,3-propanediol oxidoreductase, and hydroxyacyl-CoA transferase can be expressed in a host capable of producing glycerol from central metabolic intermediates.

Applicants' claims define a recombinant organism selected from the group consisting of bacteria, yeast, fungi, and plants comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and PHA synthase. A CoA-dependent aldehyde dehydrogenase can serve to convert propionaldehyde directly to propionyl-CoA, thus alleviating the need for a separate CoA synthetase or transferase, and avoiding the production of free propionic acid in the

cytosol (see the specification at page 8, lines 27-30). As shown in Figure 1 of the specification, the conversion of propionaldehyde to propionate is carried out by the non-CoA-dependent aldehyde dehydrogenase (also depicted in Figure 1 in Skraly, and disclosed in Toth).

Toth does not disclose a recombinant organism comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogense and a PHA synthase. A skilled artisan combining Toth and Skraly would not arrive at the recombinant organism claimed by the Applicants, because neither Toth nor Skraly separately, or in combination, recite each element of the claims. Skraly does not suggest or disclose a recombinant organism comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogense and a PHA synthase. Toth purified a CoA-acylating aldehyde dehydrogenase from *Clostridium beijerinckii*, whose sequence was compared to the aldehyde dehydrogenase from other species, and found to be most similar to the eut-encoded acetaldehyde dehydrogenases of *S. typhinurium* and *E. coli*. Skraly does not disclose or suggest the claimed organisms. Skraly discloses that an aldehyde dehydrogenase optionally can be expressed in a host. There is no mention of a CoA-dependent aldehyde dehydrogenase in Skraly, nor of a recombinant organism comprising a gene encoding this protein.

None of the prior art, either separately or in combination, lead a person of ordinary skill in the art to combine the references. Skraly discloses the pathway for the production of PHA intermediates from glycerol that involves the conversion of the intermediate propionaldehyde to the propionate by aldehyde dehydrogenase, which is converted by CoA transferase to propionyl-CoA, for subsequent conversion to 3-hydroxyvaleryl-CoA (depicted in Figure 1). Skraly does not disclose the possibility or advantages of circumventing the step wherein free propionic acid is generated in the cells. As stated in the specification on page 3, lines 18-20, propionic acid is toxic to cells and therefore reduces the rate of growth and polymer production. Without this

disclosure in Skraly, there would be no motivation for the skilled artisan to combine Skraly who discloses the optional possibility of using a non-CoA-dependent aldehyde dehydrogenase, with Toth, who teaches a CoA-dependent aldehyde dehydrogenase.

35 U.S.C. 103 is very clear: the prior art must disclose the claimed elements and the prior art must provide the motivation to combine as applicant has done, with a reasonable expectation of success. Neither Skraly nor Toth either alone or in combination meet these criteria. Therefore, claims 16-20 and 22-23 are not obvious over Skraly in view of Toth.

Skraly in view of Goodlove

Goodlove discloses the isolation, cloning and sequencing of a 6-kb fragment of DNA from *E. coli* comprising both alcohol dehydrogenase and CoA-linked acetaldehyde dehydrogenase activities. Goodlove does not suggest or disclose a recombinant organism comprising a gene encoding aldehyde dehydrogenase and a PHA synthase. A skilled artisan combining Skraly and Goodlove, would not arrive at the claimed recombinant organism because none of the references either separately or in combination recite all of the claimed limitations. Furthermore, as previously stated, Skraly does not disclose the possibility or advantages of circumventing the step wherein free propionic acid is generated in the cells. There would therefore be no motivation for a skilled artisan to combine Skraly and Goodlove. Therefore, claims 16 and 18-22 are not obvious over Skraly in view of Goodlove.

Allowance of claims 16-23 and rejoinder and allowance of claims 1-12 and 24-35 is respectfully solicited.

Respectfully submitted,

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